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COMMENTS AND CONTROVERSIES

Immortal Life of the Common Rule: Ethics, Consent, and the Future of Cancer Research

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INTRODUCTION

The advent of the first immortal human cancer cell line in 1951 (HeLa) had profound implications for cancer research.[1] Historically, the list of translational cancer research discoveries generated from human-derived cancer cell lines such as HeLa cannot be overstated.[2-4] In addition, the future of the research enterprise undoubtedly depends on continued access to the biospecimens that generate such lines. However, it was the 2010 book, *The Immortal Life of Henrietta Lacks*, and its compelling story of the woman behind HeLa, that initiated an impassioned debate on the ethics and limits of research with such tissue.[5] Applied laboratory scientists have a moral and ethical obligation to respect and honor the person from whom biospecimens were derived, but how that respect should be demonstrated is a matter of debate.

The Common Rule, initially adopted in 1991, created an overarching guideline for federally funded human subjects research to provide oversight both in response to prior ethical transgressions and to present a unified ethical and regulatory framework for the future. But, in the ensuing years, the research landscape has dramatically changed in ways that could not be anticipated two decades past. Thus, a contemporary update to the Common Rule has been long overdue. After almost 6 years of careful analysis and vetting, along with public commentaries and spirited debate, 16 federal departments and agencies, including the US Department of Health and Human Services, published the eagerly anticipated final rule for the Federal Policy for the Protection of Human Research Subjects (Common Rule) on January 18, 2017, with a plan for implementation in 2018.[6-8]

The field of cancer research is currently in a watershed, further stimulated by the Cancer Moonshot and Precision Medicine Initiative. The pace of discoveries with immediate translational potential, particularly with regard to tumor biology/immunology and genomics, is frenetic. The translation of new laboratory data to applications at the bedside has never been more dynamic or fluid. Much of this research falls under the purview of the Common Rule and is accordingly dependent on and accountable to its stipulations and revisions.

The goals of the Common Rule revisions include to "enhance respect and safeguards for research participants and to increase research efficiency by reducing unnecessary burdens and calibrating oversight to the level of risk."[9(p2293)] However, many stakeholders were concerned that several proposed changes would hinder the research enterprise unnecessarily, particularly in the field of oncology. For example, the proposed Common Rule changes in the notice of proposed rulemaking (NPRM), which preceded the final rulemaking, included efforts to require broad consent for all research with biospecimens. Under the previous version, biospecimen informed consent was only required if identifying information accompanied the sample.[6] The intent of the proposal—which considers any human tissue to be a human subject triggering informed consent protections—was to respect participant autonomy, but it raised the possibility of serious unintended consequences. A lively discussion ensued regarding how best to balance the need to protect and respect current participants who provide their tissue to advance scientific knowledge while ensuring scientists have the ability to advance science for future patients using invaluable biologic specimens.[9-11] Ultimately, the final Common Rule was receptive to such criticisms (Table 1).[13]

Herein, we summarize the revisions to the Common Rule and specifically highlight its implications for cancer research with regard to the definition of a human subject, time-limited consent, and the status of biospecimens already collected before the rules were revised. We use our own research platform to illustrate the practical impact of both the proposed and ultimately finalized changes, and speculate on how the oncology community will use this opportunity to evolve and adapt accordingly.

THE HUMANITY OF A BIOSPECIMEN: OUR LABORATORY'S DILEMMA

In the arena of human tissue research (including cancer cell line and tissue xenograft development and study), the original Common Rule established our current framework. In our translational oncology laboratory at the University of Michigan, more than 100 human cell lines and patient-derived xenografts representing head and neck cancers of various stages and subsites have been developed. These models have been distributed to institutional review board (IRB)–approved researchers throughout the world and have played key roles in advancing cancer therapeutics for the past four decades. The procurement of tumor specimens from our patients for cell line and tissue xenograft development adheres to

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Table 1. Summary of Major Changes to the Final Common Rule

Changes Not Adopted From the NPRM	Changes Adopted in the Final Rule
The final rule does not adopt the proposal to require that research involving nonidentified biospecimens be subject to the Common Rule and that consent would need to be obtained to conduct such research.	Establishes new requirements regarding the information that must be given to prospective research subjects as part of the informed consent process.
To the extent some of the NPRM proposals relied on standards that had not yet been proposed, the final rule either does not adopt those proposals or includes revisions to eliminate such reliance.	Allows the use of broad consent (ie, seeking prospective consent to unspecified future research) from a subject for storage, maintenance, and secondary research use of identifiable private information and identifiable biospecimens. Broad consent will be an optional alternative that an investigator may choose instead of, for example, conducting the research on nonidentified information and nonidentified biospecimens, having an IRB waive the requirement for informed consent or obtaining consent for a specific study.
The final rule does not expand the policy to cover clinical trials that are not federally funded.	Establishes new exempt categories of research on the basis of their risk profile. Under some of the new categories, exempt research would be required to undergo limited IRB review to ensure that there are adequate privacy safeguards for identifiable private information and identifiable biospecimens.
The final rule does not adopt the proposed new concept of "excluded" activities. Generally, activities proposed to be excluded are now either described as not satisfying the definition of what constitutes research under the regulations or are classified as exempt.	Creates a requirement for US-based institutions engaged in cooperative research to use a single IRB for that portion of the research that takes place within the United States, with certain exceptions. This requirement becomes effective 3 years after publication of the final rule.
The proposed revisions to the exemption categories have been modified to better align with the long-standing ordering in the final rule. The final rule does not include the proposed requirement that exemption determinations need to be made in specified ways.	Removes the requirement to conduct continuing review of ongoing research for studies that undergo expedited review and for studies that have completed study interventions and are merely analyzing study data or involve only observational follow-up in conjunction with standard clinical care.
The final rule does not include the proposed standardized privacy safeguards for identifiable private information and identifiable biospecimens. Aspects of proposals that relied on those safeguards have been modified or are not being adopted.	
The final rule does not adopt the most restrictive proposed criteria for obtaining a waiver of the consent requirements relating to research with identifiable biospecimens.	

NOTE. Adapted from the Federal Register.[12]
Abbreviations: IRB, institutional review board; NPRM, notice of proposed rulemaking.

the Common Rule and involves an informed consent procedure in accordance with our IRB-approved protocols.

Our cancer cell lines and xenografts are derived from patients who have undergone extensive informed consent procedures. An investigator sits down with each patient and details the process of tumor specimen collection, study goals, risks and benefits of study participation, guarantee of privacy and confidentiality, and any commercial interests that may be garnered from the patient's samples.[14] The time required for this consent process is substantial and includes an assessment of the patient's comprehension of the information provided. However, although this is our current procurement process, many additional biospecimens are included within our tissue banks and microarrays for analysis that were collected long ago without study-specific explicit consent.

The proposed expansion of the definition of a human subject by the NPRM brought our ongoing use of previously established cancer cell lines, biospecimens, and archived tissue for secondary analysis into question. Some argued that human tissue removed during the course of clinical procedures without explicit research consent and studied de-identified (ie, with no attached identifiers) is ethically defensible and associated with minimal risk.[15,16] However, such dilemmas in light of Henrietta Lacks' paradigm continued to raise questions of how best to balance privacy, consent, and scientific advancement.[17]

In effect, the final rule clarified terminology but kept the spirit of the initial version without drastically redefining what Common Rule agencies consider a human subject. The final rule recognizes the need to continually reassess how new technology may affect privacy. Agencies that implement the Common Rule are now required to consider what an "identifiable biospecimen" means at least every 4 years and are required to publish a list of what new technologies could generate "identifiable private information" from otherwise nonidentified biospecimens.

The debate over the previous iterations of the Common Rule revisions are critical to understanding the future impact of this final rule. Three areas specifically would have had profound implications for our laboratory: whether nonidentified biospecimens needed broad consent, whether biospecimens or nonidentified information would only be allowed to be collected up to 10 years after broad consent is obtained for secondary research, and whether existing specimens in biorepositories would be grandfathered in under the new rules.

BROAD CONSENT

The most controversial modification proposed by the NPRM was that "the definition of human subject be expanded to include all biospecimens, [as such] the NPRM proposes to facilitate research using biospecimens by permitting broad consent be obtained for their storage or maintenance for secondary research" (Section II, B, 2).[8(p53973)] This was a major change from the original rule, which only required consent for research with identifiable data or biospecimens.

But, as some posited, implementation of this universal broad consent requirement seemed unrealistic, akin to using a blunt tool to comprehensively address the intricacies and

nuances of an ever-increasing range of research platforms.[11] Stakeholders were also concerned about the feasibility of one broad consent being sufficiently informative, flexible, and applicable in all research scenarios.

The proposed broad consent for the secondary research use of nonidentified biospecimens "need not be study-specific, and could cover open-ended future research."[8(p53972)] Furthermore, the NPRM argued that such a broad consent procedure would be "brief,"[8(p53972)] yet would effectively protect patient autonomy and adequately ensure patient understanding of risks, benefits, and goals of secondary research use of their tissue. But there was significant uncertainty and concern over whether this type of consent would actually provide useful additional information to the participant, such that it was worth the burden of procuring it, or simply be one more piece of paper a patient signs without fully comprehending its significance.

Many were concerned about the financial costs of this additional layer of broad consent, which would have required implementation into systems, staff time to procure from patients, and expensive efforts to track specimens properly through the system. For example, the Dean of Administration of Weill Cornell Medical College estimated that it would cost as much as $4 million annually to implement all revisions.[18]

Ultimately, the Common Rule agencies cited public feedback in their change of perspective. The final rule allows for institutional flexibility within the government regulations, affording improved personalization for each institution's goals and under management of each institution's IRB.[19] Notably, much of the concern for the potential cost of applying broad consent to previously obtained biospecimens was mitigated by the ultimate decision not to expand enforcement of the Common Rule to nonidentified specimens.

Citing the Federal Plain Language guidelines (Federal Plain Writing Act of 2010), the rulemaking agencies also stressed the importance of providing consent in an understandable fashion.[20] The final rule allowed flexibility to customize consents, with guidance encouraging dissemination of sufficient information in understandable language. The final rule recognized these challenges, including the importance of pre-enrollment and pretest counseling within the constraints of clinical research platforms.

TIME-LIMITED CONSENT

Another key change initially proposed by the NPRM was that "broad consent for the research use of biospecimens . . . would be limited to covering biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained" (Section II, B, 2).[8(p53973)] The rationale for such a change included the fact that the state of the science, available techniques, and the implications thereof are dynamic. Thus, neither researchers nor participants can reasonably anticipate how their tissues might be used in the future, and likely even less so after a decade has passed, and what that might mean in a practical sense.

The proposal to limit informed consent to 10 years raised the possibility of being unable to use well-established cell lines and other biospecimens from patients with cancer in the future. Most interpreted the NPRM to indicate that it would apply to research initiated more than a decade after biospecimen collection but would exclude continuation of ongoing projects (ie, that "the period of time which biospecimens or information *collection* will occur cannot exceed 10 years" (emphasis added).[8(p54053)] But the nature of cell lines confuses such rhetoric because of their immortality and ability to remain viable after years (or decades) in a freezer. Many of the concerns with HeLa reflected the fact that cell lines are a special category and might be considered (both in an ethical and regulatory sense) differently than other biospecimens. Even the DNA of a cell line is related (but distinct) from its parent tumor, confusing the question of ownership as well as practical identifiability. A cell line might be shared (or sold) to researchers at other institutions or used in dramatically different ways than might have been intended when they were obtained. Thus, the 10-year rule might be conceptualized differently for cells that have the potential to live and grow indefinitely, rather than formalin-fixed specimens that are truly "dead."

The majority of the patients from whom our cell lines are derived have succumbed to their disease or competing mortalities. The donors for University of Michigan (UM) Squamous Carcinoma cell lines (SCC)-1 through UM-SCC-81 are all deceased, most within 2 years of tissue procurement, and UM-SCC-1 is still being routinely used by researchers throughout the world.[21-23] In addition, at a tertiary care center, many patients transition their care back within their community and may be lost to follow-up. Thus, it would be difficult, if not impossible, to contact and reconsent individuals after 10 years.

The value of cancer cell lines only increases with time as their genetic aberrations and phenotypes are better characterized. The proposed scenarios could have put a time-stamp on such cell lines after significant amounts of research effort and grant money would have been dedicated to their study. Generating data and using tissue from established cancer cell lines and preserved tumor specimens, perhaps years after the date of procurement, would have faced significant obstacles.[10] Given the importance of these biospecimens as the foundation of much of cancer research, these proposals threatened to change the core of how oncology research could be performed. The prospect of discarding such highly valuable biologic material after a seemingly arbitrary time interval was troubling. What was worrisome was how a proposed time limit on informed consent could have effectively handcuffed the generation and subsequent study of cancer cell lines and related research on previously procured specimens from patients who presumably very much wanted research into therapies continued. In addition, specific models of specific diseases may be difficult to derive (including orphan cancers as well as common malignancies that are difficult to establish, such as prostate cancer), so that entire fields of research may be dependent on a handful of cell lines.[24-26]

As would be anticipated, there was considerable criticism of the NPRM proposal for a 10-year limit on consent in line with these issues. Ultimately, the Common Rule agencies appreciated the importance of continued use of biospecimens, and the final rule did not include the proposed 10-year limit to consent, with an extended discussion of public feedback and the rationale for the rejection of this component of the NPRM.

GRANDFATHERED BIOSPECIMENS

Lastly, a significant concern was raised with regard to the potential limitations and obstacles imposed on generating data and using

tissue from preserved tumor specimens, perhaps years after the date of procurement.[10] The announcement preceding the NPRM (called the Advanced Notice of Proposed Rulemaking) asked whether previously existing biospecimens and data should be grandfathered under the prior regulatory requirements or subjected to the new changes.[7] The NPRM implied that previously adopted tissues would not be subject to new or updated regulations, but it remained unclear how this would be implemented in the final rule. For example, the adoption of the proposed NPRM definition had the potential to limit our ability to continue to use our already established cell lines. Notably, there was also significant concern over the potential for handcuffing and limiting next-generation sequencing of tumors and precision medicine, both of which are at the forefront of modern cancer care.

In response to the proposal to expand the definition of human subject to include nonidentified biospecimens, the majority of commenters expressed opposition to this change.[18] The preamble to the final rule noted the significant commenter concern about the limitations that the proposed definition changes would place on research practices and potential discoveries. One of the public comments was collectively submitted by ASCO, the American Association for Cancer Research, the Association of American Cancer Institutes, and the American Society for Radiation Oncology and urged reconsideration of three major components of the NPRM, articulating their rationale accordingly:

1. The proposed classification of all biospecimens as "human subjects," regardless of whether the biospecimens contain identifiable information.
2. The lack of clear and consistent privacy standards across all research, including possible confusion between the HIPAA Privacy Rule and the Common Rule.
3. The absence of harmonized guidelines for reporting unanticipated problems and adverse events and the decision to abandon a harmonized electronic database for reporting.[27(p2-4)]

The final rule removed the requirement for consent for nonidentified biospecimens. This is a critical change and permits cancer researchers to analyze existing and prospectively procured de-identified specimens. It also allows for secondary analysis of identified biospecimens procured outside of research, for example, clinically, if researchers receive a waiver or satisfy other specific exemption criteria, such as getting broad consent for storage, maintenance, and secondary use.[19]

THE FUTURE

The Common Rule agencies have thoughtfully addressed the public comments of a litany of stakeholders in their consideration and ultimate revision of the proposed Common Rule; its influence on our laboratory is but a microcosm of its national impact. Of course, the process is imperfect; the final Common Rule is not a panacea, the process was prolonged, and inevitable compromises were required. But in essence, this is an illustration of the federal government doing its job.

The fact that the Common Rule did not redefine a "biospecimen," but rather added new definitions for "identifiable private information" and "identifiable biospecimen," carries weight moving forward. Within a year of implementation (and at least every 4 years thereafter), regulations now stipulate that "appropriate experts" must reassess these definitions in light of emerging data and technology. For example, in the future, it is conceivable that cell lines could be relabeled identifiable biospecimens, which may require additional consent processes, or that specific analytic technologies or techniques (such as whole genome sequencing) might be considered to have the ability to generate identifiable private information such that their use might be restricted. Of course, how these definitions will be assessed in the future cannot be known, but the research community must anticipate ongoing reassessment of what is "identifiable," so what is permissible will remain a moving target.

There are, of course, other uncertainties. The US Department of Health and Human Services is under Executive Branch oversight, and the final Common Rule is not slated to take effect for another year. The presidential administration, as well as Congress, have promised significant changes and reconsideration, if not blanket rejection, of many of the preceding administration's executive actions. It is unknown whether the final Common Rule will be enabled, edited, or rejected outright.

For oncologists and cancer researchers, the uncertain future of the Common Rule will inevitably lead to concern, both regarding current practices and future protocols. After years of deliberation and a long-overdue contribution to the existing regulatory landscape, defaulting to a 1991 baseline and erasing years of thoughtful effort is a disheartening prospect. The current leadership's promises to undo or perhaps dismantle the culmination of almost 6 years of thoughtful consensus will only lead to unsettlement, exasperation, and confusion that would undo a carefully crafted bipartisan effort. Of course, the future of the Cancer Moonshot and National Institutes of Health funding itself similarly remains uncertain and privy to the whims of our elected officials. We are in polarizing times; our hope is that the political climate will not adversely affect the scientific community's mission to address, prevent, and treat the diseases that continue to constitute the greatest common threat to humanity and respect the participants who enable that work.

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REFERENCES

1. Gey GO, Coffman WD, Kubicek MT: Tissue culture studies of the proliferative capacity of cervical carcinoma and normal epithelium. Cancer Res 12: 264-265, 1952

2. Turner T: Development of the polio vaccine: A historical perspective of Tuskegee University's role in mass production and distribution of HeLa cells. J Health Care Poor Underserved 23:5-10, 2012 (4, suppl)

3. zur Hausen H, Gissmann L, Steiner W, et al: Human papilloma viruses and cancer. Bibl Haematol 43:569-571, 1975

4. Greider CW, Blackburn EH: Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. Cell 43:405-413, 1985

5. Skloot R: The Immortal Life of Henrietta Lacks. New York, NY, Broadway Paperbacks, 2011

6. US Department of Health and Human Services: 45 CFR 46. Code of Federal Regulations. Title 45. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subparta

7. US Department of Health and Human Services: Department of Health and Human Services. Office of the Secretary. 46 CFR Parts 46, 160, and 164. https://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18792.pdf

8. US Department of Health and Human Services: Federal Register. Vol. 80 No. 173. Tuesday, September 8, 2015. https://www.gpo.gov/fdsys/pkg/FR-2015-09-08/pdf/2015-21756.pdf

9. Hudson KL, Collins FS: Bringing the Common Rule into the 21st century. N Engl J Med 373:2293-2296, 2015

10. Grizzle WE: Missed opportunities and lost lives: Consequences of some proposed changes to regulations on research with human tissues–letter. Clin Cancer Res 21:5404-5405, 2015

11. Lo B, Barnes M: Federal research regulations for the 21st century. N Engl J Med 374:1205-1207, 2016

12. Federal Register: Federal Policy for the Protection of Human Subjects. https://federalregister.gov/d/2017-01058

13. Menikoff J, Kaneshiro J, Pritchard I: The Common Rule, updated. N Engl J Med 376:613-615, 2017

14. University of Michigan Comprehensive Cancer Center: The Head and Neck SPORE Program. http://www.med.umich.edu/cancer/hn-spore/

15. Wilson D: A troubled past? Reassessing ethics in the history of tissue culture. Health Care Anal 24:246-259, 2016

16. The American Society of Human Genetics: ASHG report. Statement on informed consent for genetic research. Am J Hum Genet 59:471-474, 1996

17. Hodge JG, Gostin LO: Revamping the US Federal Common Rule: Modernizing human participant research regulations. JAMA 10.1001/jama.2017.1633 [epub ahead of print on February 22, 2017]

18. Glimcher LH: How not to end cancer in our lifetimes https://www.wsj.com/articles/how-not-to-end-cancer-in-our-lifetimes-1459811684.

19. US Department of Health and Human Services: Department of Homeland Security. 6 CFR Part 46. https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf

20. United States Congress: Public Law 111-274. 111th Congress. https://www.gpo.gov/fdsys/pkg/PLAW-111publ274/pdf/PLAW-111publ274.pdf

21. Krause CJ, Carey TE, Ott RW, et al: Human squamous cell carcinoma. Establishment and characterization of new permanent cell lines. Arch Otolaryngol 107:703-710, 1981

22. Kumar D, Kandl C, Hamilton CD, et al: Mitigation of tumor-associated fibroblast-facilitated head and neck cancer progression with anti-hepatocyte growth factor antibody ficlatuzumab. JAMA Otolaryngol Head Neck Surg 141: 1133-1139, 2015

23. Misawa Y, Misawa K, Kanazawa T, et al: Tumor suppressor activity and inactivation of galanin receptor type 2 by aberrant promoter methylation in head and neck cancer. Cancer 120:205-213, 2014

24. Horoszewicz JS, Leong SS, Kawinski E, et al: LNCaP model of human prostatic carcinoma. Cancer Res 43:1809-1818, 1983

25. Udager AM, Rolland DC, McHugh JB, et al: High-frequency targetable EGFR mutations in sinonasal squamous cell carcinomas arising from inverted sinonasal papilloma. Cancer Res 75:2600-2606, 2015

26. Lee C, Shevrin DH, Kozlowski JM: In vivo and in vitro approaches to study metastasis in human prostatic cancer. Cancer Metastasis Rev 12:21-28, 1993

27. US Department of Health and Human Services: Federal Policy for the Protection of Human Subjects. http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/Comments_Common_Rule_ANPRM_ASCO_AACR_AACI_FINAL___F3F578.pdf

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